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(71) Applicant: 000113470
Pola Chemical Industrial Company, Ltd.
6-48 Yayoi-cho, Shizuoka-shi, Shizuoka-ken

(72) Inventor: Shigeharu Tanizawa
c/o Yokohama Research Laboratories
Pola Chemical Industrial Company, Ltd.
27-1 Takashimadai, Kanagawa-ku, Yokohama-shi, Kanagawa-ken

(72) Inventor: Chihoko Suga
c/o Yokohama Research Laboratories
Pola Chemical Industrial Company, Ltd.
27-1 Takashimadai, Kanagawa-ku, Yokohama-shi, Kanagawa-ken

(54) **[Title of the Invention] An Adrenocortical Hormone Secretion Inhibitory Agent**

(57) [Abstract]

[Structure] An adrenocortical hormone secretion inhibitory agent comprised of essence of plants of the family Labiatae and compositions of cosmetics, medicinal drug products and food products that contain them.

[Effect] Because excess secretion of adrenocortical hormone is inhibited by means of this invention, vascular impairment caused by it is prevented.

[Claims]

[Claim 1]
An adrenocortical hormone secretion inhibitory agent comprised of essence of plants of the genus Labiatae.

[Claim 2] An adrenocortical hormone secretion inhibitory agent as described in Claim 1 in which the plant of the family Labiatae may be lavender, marjoram, thyme, sage, basil, peppermint, spearmint, rosemary, catnip, lemon palm, oregano, Japanese mint and beefsteak plant.

[Claim 3] An adrenocortical hormone secretion inhibitory agent as described in Claims 1 or 2 in which the essence is a component in the plant body having a melting point less than 200°C.

[Claim 4] An adrenocortical hormone secretion inhibitory agent as described in any one of Claims 1 to 3 in which the adrenocortical hormone is cortisol.

[Claim 5] An adrenocortical hormone secretion inhibitory agent as described in any one of Claims 1 to 4 in which the secretion of the adrenocortical hormone is by way of secretion in saliva.

[Claim 6] A stress relaxant that is comprised of the adrenocortical hormone secretion inhibitory agent described in any one of Claims 1 to 5.

[Claim 7] A composition that contains one or two or more substances selected from the stress relaxant described in Claim 6.

[Claim 8] A composition that contains the adrenocortical hormone inhibitory agent described in any one of Claims 1 to 5.

[Detailed Description of the Invention]

[0001]

[Technological field of the invention] This invention relates to an adrenocortical hormone secretion inhibitory agent, a stress relaxant and a composition that contains them.

[0002]

[Prior art] No one can deny that the present time is an age of stress and those that live in modern societies live lives in which they are subjected to excessive stress. For this reason, the typical diseases of modern people are psychosomatic conditions such as anorexia, insomnia, hyperphagia, neurosis and refusal to go to work. Although karaoke and so-called nominication [TRANSLATOR's NOTE: This appears to be a made-up word based on the word "communication" using 'nomi" = drinking, instead of "commu" =; a good equivalent might be "communal drinking"] is widely practiced in order to reduce these stresses, it goes without saying that these measures are not healthy. Sports are also a means for dissipating stress. However, moderate participation in sports when one is very busy is either of little effect or presents a considerable danger of bringing on a heart attack. From this standpoint, a means for reducing stress without being immoderate is sought.

[0003] There are two types of adrenocortical hormones, glucocorticoids and mineralocorticoids and they are said to play various roles. For example, glucocorticoids promote sugar production in the liver, elevating blood sugar levels. In muscle, they promote breakdown of protein, and, in adipose tissue, they pr mote breakdown of fat, increasing the quantity of free fatty acids in the blood. In addition, they inhibit edema, capillary dilation, fibrin deposition, neutrophil migration, phagocytic action, proliferation of fibroblasts and granulation due to inflammation. Mineralocorticoids act on the distal urinary tubules of the kidneys, promoting reabsorption of sodium and promoting urinary excretion of potassium and

hydrogen ions. Of the two, it is said that glucocorticoids are substances that are highly involved in stress and it is said that the quantity of secretion of glucocorticoids into the blood is increased when stress is strongly felt. However, it is not known what effect the presence of senna fragrance has on body fluid concentrations of glucocorticoids in states of high stress.

[0004] Although it is said that fragrances, of which senna is representative, have an anti-stress effect, no instances are known in which such an effect has actually been confirmed. In addition, there has been no quantification of the positive stress effects of senna. Moreover, it is not known whether senna has the anti-stress action or the superior glucocorticoid decreasing action of plants of the family Labiatae.

[0005]

[Problems the invention is intended to solve] This invention was developed under these circumstances and has the objective of providing an adrenocortical hormone secretion inhibitory agent which inhibits the secretion of adrenocortical hormones, which is a convenient index of stress, and which lowers the concentration of adrenocortical hormone in body fluids.

[0006]

[Means for solving the problems]. In the light of these circumstances, the inventors conducted repeated screening studies of various raw materials in order to find an adrenocortical hormone secretion inhibitory agent which inhibits the secretion of adrenocortical hormones, which is a convenient index of stress, and which lowers the concentration of adrenocortical hormone in body fluids. As a result, they perfected this invention by discovering such an action in essence of plants of the family Labiatae.

(0007) (1) Adrenocortical hormone secretion inhibitory agents of this invention

The adrenocortical hormone secretion inhibitory agents of this invention are comprised of essence of plants of the family Labiatae. Plants of the family Labiatae include, for example, lavender, marjoram, thyme, sage, basil, peppermint, spearmint, rosemary, catnip, lemon palm, oregano, Japanese mint and beefsteak plant. It can be anticipated that any of them have an adrenocortical hormone secretion inhibitory action. Of these, lavender, marjoram, mint and basil are preferable, and, among the latter, lavender, mint and basil are particularly desirable. The term essence that is referred to in this invention is a general term referring to processed products that are obtained by drying, finely cutting and pulverizing the bodies of these plants, extracts obtained by extracting the plant body or processed product thereof with a solvent and removing the solvent from the extracted material, distilled products obtained by distillation or steam distillation of plant bodies or processed products thereof and refined products obtained by subjecting extracts or distilled substances to column chromatography or solution extraction. Here, steam distillation may be performed in the usual way by blowing steam at the plant body or processed product thereof, cooling the matter that is distilled out and separating it into the aqueous phase and the organic phase and collecting the organic phase. Extraction may be performed over a period of several days when the solvent is added to the plant body or processed product thereof in an amount of 0.5 to 10 times its volume and the materials are at room temperature or may be performed by immersion for several hours when the temperature is close to the boiling point. Solvents that can be cited include, for example, alcohols such as methanol and ethanol, esters such as ethyl acetate and methyl acetate, nitriles such as acetonitrile, ethers such as diethyl ether and tetrahydrofuran, halogenated hydrocarbons such as chloroform and methylene chloride and ketones such as acetone and methyl ethyl ketone. Any of these substances can be used in this invention. However, of these, among the plant structural components obtained by distillation, low boiling point components, i.e., components with b iling points less than 200°C, are preferable. The reason for this is that a safe adrenocortical hormone secretion inhibitory action can be anticipated most effectively in cases in which the adrenocortical hormone secretion inhibitory agent of this invention is stimulated through the sense of smell by means of fragrances. The adrenocortical hormone secretion inhibitory agent of this invention, as shown in the examples to be described subsequently, has the action of lowering the concentration of the adrenocortical hormones in the saliva through the agency of the sense f smell.

[0008] (2) Relationship between stress load and adrenocortical hormones

Although there is a deep relationship between stress and adrenocortical hormones, and, especially, with glucocorticoids, there are no examples in which these relationships have actually been confirmed. Using cortisol as the glucocorticoid, the following experiment was performed in order to ascertain the relationship between stress load and cortisol. Specifically, twenty test subjects were assembled, calculations of mathematical operations were performed to two places for 30 minutes with a delay of 4 seconds per problem. Saliva was collected 30 minutes before and after and the cortisol concentration in the saliva was found by radioimmunoassay, which indicates the state of execution of this invention to be described subsequently. The percentage of cortisol added to the saliva was found by the following calculation: (concentration of cortisol after calculation – concentration of cortisol before calculation)/(concentration of cortisol before calculation) * 100. Similarly, these values were found on other days when the delay time was set to 3 seconds and when the time for solving the problem was set to 40 minutes. The results are shown in Table 1. From this table, it can be seen that the percentage of cortisol added increased proportionally to the amount of cortisol load. Specifically, it was found that the amount of secretion of glucocorticoid, of which cortisol is representative, into the saliva can serve as an index of the intensity of stress. That is, it can be said that a substance that decreases the amount of secretion of glucocorticoid of which cortisol is representative is a substance that can reduce stress.

[0009]

[Table 1]

Conditions	Average percentage of cortisol added (%)
Delay of 4 seconds; 30 minutes	43
Delay of 3 seconds; 30 minutes	62
Delay of 4 seconds; 40 minutes	56

[0010] (3) Action of the adrenocortical hormone secretion inhibitory agent of this invention

The adrenocortical hormone secretion inhibitory agent of this invention has the action of relaxing stress by means of stimulating the sense of smell as a fragrance. As a result, it has the actions of inhibiting the secretion of adrenocortical hormone in saliva and lowering its concentration. The adrenocortical hormone secretion inhibitory agent of this invention acts as a fragrance. The use amount at which this effect is manifested is 0.01 to 10 mg/m^3. This is desirable because the sense of smell is stimulated at this concentration. The source plants of this invention are all widely used as foods so that there is no worry about them displaying toxicity at these concentrations.

[0011] (4) The composition of this invention

The composition of this invention is characterized in that it contains the adrenocortical hormone secretion inhibitory agent described above. There are no particular limitations on the type of composition as long as the stimulation by the adrenocortical hormone secretion inhibitory agent of this invention is transmitted via the sense of smell. For example, it may be in the form of a fragrant product such as potpourri, a ro m fragrance, perfume or toilet water, a food product such as gum or candy or a

beverage such as juice or cold drinks. Any desired component that is ordinarily used in such compositions can be used in the composition of this invention in addition to the adrenocortical hormone secretion inhibitory agent. Such components in fragrant products can include, for example, hydrocarbons such as vaseline and microcrystalline waxes, esters such as jojoba oil and spermaceti, triglycerides such as tallow and olive oil, higher alcohols such as cetanol and oleyl alcohol, fatty acids such as stearic acid and oleic acid, polyvalent alcohols such as glycerol and 1,3-butanediol, nonionic surfactants, anionic surfactants, cationic surfactants, amphoteric surfactants, thickeners such as ethanol and carbobol [sic], preservatives, ultraviolet ray absorbents, antioxidants, pigments and powders. In food products and beverages, they can include flavor and odor enhancing agents, sweeteners, acid flavoring agents, oils and fats, thickeners, emulsion stabilizers, water, carbonic acid, excipients and binders. The desirable content of the adrenocortical hormone secretion inhibitory agent of this invention in these compositions in fragrant products is 0.01 to 60 weight %, more preferably, 0.05 to 40 weight %, and, most preferably, 0.1 to 30 weight %. In food products or beverages, it is 0.01 to 30 weight %, more preferably, 0.05 to 20 weight %, and, most preferably, 0.01 to 10 weight %. These compositions can be manufactured by any known method.

[0012]

[Mode of execution of the invention] We shall now present a detailed description of the mode of execution of this invention by presenting examples. However, it goes without saying that this invention is not limited solely to these examples.

[0013] Example 1 (Example of Manufacture)

1 kg of whole dried leaves of lavender was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.7 g of adrenocortical hormone secretion inhibitory agent 1 was obtained.

[0014] Example 2 (Example of Manufacture)

1 kg of dried leaves of peppermint was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 1.1 g of adrenocortical hormone secretion inhibitory agent 2 was obtained.

[0015] Example 3 (Example of Manufacture)

1 kg of dried leaves of spearmint was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.8 g of adrenocortical hormone secretion inhibitory agent 3 was obtained.

[0016] Example 4 (Example of Manufacture)

1 kg of dried leaves of marjoram was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.7 g of adrenocortical hormone secretion inhibitory agent 4 was obtained.

[0017] Example 5 (Example of Manufacture)

1 kg of dried leaves of basil was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 1.2 g of adrenocortical hormone secretion inhibitory agent 5 was obtained.

[0018] Example 6 (Example of Manufacture)

1 kg of dried leaves of lemon palm was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.9 g of adrenocortical hormone secretion inhibitory agent 6 was obtained.

[0019] Example 7 (Example of Manufacture)

1 kg of dried leaves of sage was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.8 g of adrenocortical hormone secretion inhibitory agent 7 was obtained.

[0020] Example 8 (Example of Manufacture)

1 kg of dried leaves of rosemary was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 1.3 g of adrenocortical hormone secretion inhibitory agent 8 was obtained.

[0021] Example 9 (Example of Manufacture)

1 kg of dried leaves of catnip was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 1.1 g of adrenocortical hormone secretion inhibitory agent 9 was obtained.

[0022] Example 10 (Example of Manufacture)

1 kg of dried leaves of thyme was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.6 g of adrenocortical hormone secretion inhibitory agent 10 was obtained.

[0023] Example 11 (Example of Manufacture)

1 kg of dried leaves of oregano was pulverized and subjected to steam distillation. The matter insoluble in water was collected and 0.7 g of adrenocortical hormone secretion inhibitory agent 11 was obtained.

[0024] Example 12 (Example of Manufacture)

1 kg of dried leaves of beafsteak plant was pulverized and subjected to reflux for 2 hours in 3 liters of methanol. Extraction was then performed, the solvent was removed and 2.1 g of adrenocortical hormone secretion inhibitory agent 12 was obtained.

[0025] Example 13 (Example of Manufacture)

1 kg of dried leaves of Japanese mint was pulverized and subjected to reflux for 2 hours in 5 liters of methanol. Extraction was then performed, the solvent was removed and 2.5 g of adrenocortical hormone secretion inhibitory agent 13 was obtained.

[0026] Examples 14 to 20 (Compounding Examples)

Room fragrances were manufactured in accordance with the formulations shown in Table 2. Specifically, the formulation components were heated and dissolved and were poured into containers in which they were allowed to harden, with room fragrances being obtained.

[0027]

[Table 2]

Component	Example 14	Example 15	Example 16	Example 17	Example 18	Example 19	Example 20
Carnauba wax	60	50	50	50	50	50	50
Liquid paraffin	30	30	30	30	30	30	30
Example 1	10						
Example 2		10					
Example 3			10				
Example 4				10			
Example 5					10		
Example 6						10	
Example 7							10

[0028] Examples 21 to 27 (Compounding Examples)

Calm [phonetic]* fragrances were manufactured in accordance with the formulations shown in Table 3. Specifically, the formulation components were heated and dissolved, packed in containers and wicks were installed, with calm [phonetic] fragrances being obtained.

[0029]

[Table 3]

Component	Example 21	Example 22	Example 23	Example 24	Example 25	Example 26	Example 27
Ethanol	50	50	50	50	50	50	50
PEG 400	30	30	30	30	30	30	30
Example 8	10						2
Example 9		10					2
Example 10			10				2
Example 11				10			2
Example 12					10		1
Example 13						10	1

[0030] Examples 28 to 34

Toilet water was made in accordance with the formulations shown in Table 4. Specifically, the formulation components were heated and stirred at 80° and solubilized, with toilet water being obtained.

* [Translator's Note: Transliterated phonetically from the Japanese. As such, the spelling may differ from other transliterations.]

[0031]

[Table 4]

Component	Example 28	Example 29	Example 30	Example 31	Example 32	Example 33	Example 34
Ethanol	10	10	10	10	10	10	10
Propanol	6	5	5	5	5	5	5
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Tincture	82.9	82.9	82.9	82.9	82.9	82.9	82.0
Example 1	1						
Example 2		1					
Example 3			1				
Example 4				1			
Example 5					1		
Example 6						1	
Example 7							1

[0032] Examples 35 to 41 (Compounding Examples)

Hair tonics were prepared in accordance with the formulations shown in Table 5. Specifically, the formulation components were weighed out, stirred and solubilized, with hair tonics being obtained.

[Table 5]

Component	Example 35	Example 36	Example 37	Example 38	Example 39	Example40	Example 41
Ethanol	50	50	50	50	50	50	50
Propanol	5	5	5	5	5	5	5
Cayenne pepper	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Tincture	42.9	42.9	42.9	42.9	42.9	42.9	42.0
Example 8	1						0.2
Example 9		1					0.2
Example 10			1				0.2
Example 11				1			0.2
Example 12					1		0.1
Example 13						1	0.1

[0033] Examples 42 to 48 (Compounding Examples)

Candy was made in accordance with the formulations shown in Table 6. Specifically, the formulation components were heated at 120°C and made to a uniform state. They were then molded and candy was obtained.

[0034]

[Table 6]

Component	Example 42	Example 43	Example 44	Example 45	Example 46	Example 47	Example 48
White sugar	50	50	50	50	50	50	50
Thick malt syrup[**]	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5
Example 1	15						
Example 2		15					
Example 3			15				
Example 4				15			
Example 5					15		
Example 6						15	
Example 7							15

**[Translator's Note: The Japanese characters are very poorly legible]

[0035]

[Example]

Example 1

A study was conducted of the adrenocortical hormone secretion inhibitory action of adrenocortical hormone secretion inhibitory agents 1 to 13 of Examples 1 to 13. The 30-minute calculation load procedure with a delay of 4 seconds described above was performed using 20 test subjects in the presence of adrenocortical hormone secretion inhibitory agents 1 to 13. In the control group, it was performed in the absence of a fragrance. Saliva was collected before and after the procedure and quantitative determinations of cortisol were performed using gamma cortocortisol [TRANSLATOR's NOTE: This appears to be a typographical error for "gamma counter"]. Specifically, the saliva was frozen for 24 hours at -20°C and then restored to 5°C. It was then centrifuged for 15 minutes at 3000 cpm and the supernatant was collected. One vial of the tracer solution of the kit was thoroughly mixed with 100 ml of the buffer solution of the kit to make a tracer buffer solution. The antibody tubes of the kit were used respectively as the test sample and a blank and 200 μl of physiological saline solution and standard solution of cortisol were introduced. Amounts of 1 ml of tracer buffer solution were added to these tubes. Amounts of 1 ml of tracer buffer solution were added to the tubes (T1, T2) for total count determination, caps were placed on them and they were used as total count tubes. These tubes were incubated for 45 minutes at 37°C. The content solution was removed, and determinations were made of the total radioactivity of the tubes with a gamma counter. Radioactivity relative to the standard solution was plotted, a calibration curve was prepared and the concentrations of cortisol in each test sample were calculated from this calibration curve. As comparison products, leaf alcohols, which are fragrant components of forests, and linalool, which is a fragrant component of citrus fruits, were used. The results are shown in Table 7. The unit of the numerical values in the table is μg/dl. From this table, it can be seen that the adrenocortical hormone secretion inhibitory agent of this invention significantly decreased the concentration of cortisol in saliva. Further, the amount of decrease was higher than that leaf alcohols and linalool. It is also clear from the experimental results that the anti-stress effects of senna were evaluated quantitatively.

[0036]

[Table 7]

Test sample	Before the procedure	After the procedure
Cortisol	0.240	0.351
Adrenocortical hormone secretion inhibitory agent 1	0.247	0.312
Adrenocortical hormone secretion inhibitory agent 2	0.248	0.299
Adrenocortical hormone secretion inhibitory agent 3	0.250	0.284
Adrenocortical hormone secretion inhibitory agent 4	0.239	0.287
Adrenocortical hormone secretion inhibitory agent 5	0.251	0.331
Adrenocortical hormone secretion inhibitory agent 6	0.246	0.319
Adrenocortical hormone secretion inhibitory agent 7	0.255	0.335
Adrenocortical hormone secretion inhibitory agent 8	0.241	0.322
Adrenocortical hormone secretion inhibitory agent 9	0.249	0.329
Adrenocortical hormone secretion inhibitory agent 10	0.253	0.341
Adrenocortical hormone secretion inhibitory agent 11	0.235	0.333
Adrenocortical hormone secretion inhibitory agent 12	0.245	0.328
Adrenocortical hormone secretion inhibitory agent 13	0.255	0.330
Leaf alcohol	0.256	0.345
Linolool	0.240	0.339

[0037]

[Effect of the invention] By means of this invention, secretion of adrenocortical hormone, which is a convenient index of stress, can be inhibited and the concentration of adrenocortical hormone in saliva can be decreased.